L. XVII, No. 1

JANUARY-FEBRUARY, 1956

W10.5
B73

BORDEN'S REVIEW

of

NUTRITION RESEARCH

UNIVERSITY
OF MICHIGAN
APR 2[illegible]
MEDICAL
LIBRARY

NUTRITION IN VASCULAR DISEASE

BORDEN'S REVIEW
of
NUTRITION RESEARCH

Reviews and summaries of research information concerning nutrition and foods. Published bi-monthly, by THE BORDEN COMPANY; officers of the Company: Harold W. Comfort, president; E. L. Noetzel, treasurer; D. T. Orton, secretary. Editorial office: 350 Madison Avenue, New York 17, N. Y.

NUTRITION IN VASCULAR DISEASE

By LAURANCE W. KINSELL, M.D.*

Institute for Metabolic Research of the Highland Alameda
County Hospital, Oakland, California

The problem of degenerative vascular disease has become of interest to almost every individual who reads a newspaper, listens to the radio, or watches television. This excludes very few but newborn infants.

It is becoming clear that the development of atherosclerosis may be influenced by what Dr. Paul Dudley White calls "our ways of life." Certainly diet is one of "our ways of life" that has raised many provocative questions concerning the etiology of atherosclerosis. However, while diet is one of the most influential environmental factors, others, such as our increased tensions and decreased exercise, may play a part in the increase of atherosclerosis and coronary heart disease.

No attempt will be made in this review to consider the *total* problem of nutrition in relation to cardiovascular disease; e.g. beriberi heart disease. The review rather will be limited to consideration of fundamental concepts and recent investigation relating to arteriosclerosis in general, and atherosclerosis in particular. The basic questions in this field appear to be:

1. Do nutritional factors bear any relationship to atherosclerosis?
2. If so, is the nature of the relationship understood?
3. If there is a relationship, is it of major importance, or of little importance?
4. What dietary measures may result in decreased occurrence of, or improvement in, human atherosclerosis?

On the basis of extensive animal investigation, it appears that there is a significant relationship between nutrition and the development of experimental atherosclerosis. Dating from the work of Anitschkow in 1913 (1, 2), feeding cholesterol in relatively large amounts to a variety of animals has repeatedly resulted in a progressive rise in certain of the serum lipids, and subsequently in the abnormal deposition of lipids in the arterial wall (3). On the other hand, these effects have not been produced uniformly in all species of animals studied (3, 12). A conflicting literature exists as to the relationship of dietary cholesterol to serum lipid levels, and to atherosclerosis in man (4).

---

*The assistance of my associates Drs. Roger W. Friskey and Frederick R. Brown, Jr., in the preparation of this review, is gratefully acknowledged.—L. W. K.

It is not clear if the pathogenesis of human atherosclerosis involves an initial breach in the inner arterial wall with secondary deposition of lipids (13), or if the abnormal deposition of lipids is the primary lesion (14).

Rinehart and his associates have shown that experimentally induced vitamin B_6 deficiency in monkeys will result in the predictable appearance of vascular lesions (15). No lipids have been demonstrated in these lesions.

Stare and his associates (12) have produced lesions in monkeys (a species normally resistant to cholesterol-induced atherosclerosis) by administering diets deficient in methionine and cystine, but supplemented with choline. These vascular lesions are predictable and have much in common with human atherosclerosis. Administering methionine, and cystine to a lesser degree, will result in regression of the associated hypercholesterolemia.

Wilgram, Hartroft and Best have produced lesions in the cardiac musculature, the aorta, and the coronary arteries of rats (all in association with lipid deposition) by feeding high-fat, choline-deficient diets (16, 17). More recently this work has been extended by Wilgram, Best and Lewis (18).

A number of reports concern the effects of choline and methionine upon serum lipids in experimental animals and in human subjects (5). These reports are conflicting. It appears that adding either or both compounds to average diets produces only minor changes in the serum lipids in most individuals. While true choline or choline-precursor deficiency can be a factor in the etiology of experimental atherosclerosis and hypercholesterolemia, the usual American diet contains an abundance of protein, and hence of methionine. Pharmacologic amounts of methionine or choline probably produce no effect.

A variety of nutritional factors have been considered in relation to vascular disease and to lipid metabolism. Among these are:

1. Calories (hypernutrition and hyponutrition).
2. Fat.
3. Cholesterol.
4. Entities other than triglycerides present in dietary fats, particularly vegetable sterols and phospholipids.
5. Dietary protein.
6. Vitamins other than B_6.
7. Minerals, particularly as related to hypertension.

Calories

Overnutrition and obesity appear to bear a direct statistical relationship to vascular disease, particularly coronary atherosclerosis (19-22). So far as

this reviewer knows, this is one of two positive statements one is able to make at present in regard to clinical vascular disease. This statement applies in particular to males in the 40 to 60 age group and to all individuals over the age of 60. It appears not to apply to individuals under the age of 40 (6). These statistics indicate that *hereditary factors* and *endocrine factors* must receive proper emphasis in the investigation of degenerative vascular disease. The findings of Barr (23) and Katz (7) and their respective collaborators have established a significant relationship between "sex steroids" and vascular disease. The importance of hereditary factors in atherogenesis has been established by the excellent observations of Wilkinson and his colleagues (24) in patients with the heterozygous and homozygous forms of familial hyperlipemia.

Fats in general

A considerable literature suggests that a large intake of dietary fat may produce atherosclerosis. Keys and his associates in particular have been proponents of this point of view (20, 25, 26). The literature until the past few years tended to indicate that fats of all kinds were equally "bad" in this regard. Recently, Kinsell and his associates (27) have shown that chemically constant diets, containing large amounts of vegetable fat, not only produced no increase in plasma cholesterol and other lipids, but were associated predictably with a striking decrease in plasma lipids as compared to the levels on an average mixed diet. Replacement of the vegetable fat by animal fat in experimental diets, resulted in a prompt return of the lipids to levels noted on an average diet. These results have been confirmed by Ahrens et al (28), and by Beveridge et al (29). More recently, Kinsell and his associates (30, 31) have shown that the fall in serum lipids is related directly to the *degree of unsaturation* of the administered fat, *rather than to its origin from vegetable or animal sources.* Saturated vegetable fat (e.g. cocoanut oil) produces no significant lowering of serum lipids. Recent observations suggest strongly that a critical ratio exists between the amount of the essential fatty acids in the diet, and other dietary constituents, e.g. cholesterol, insofar as the level of plasma cholesterol and phospholipids is concerned (31a).

Some of these findings appear to have been confirmed by Lever and Waddell (32). These investigators administered cottonseed oil emulsion intravenously to patients with hypercholesterolemia, as well as to other individuals. In most instances, a significant decrease in serum cholesterol occurred. Cottonseed oil has an iodine number of 110-115. Kinsell and his associates

had previously reported that the intravenous infusion of a fat emulsion, made from hydrogenated cocoanut oil (iodine number 8) produced no decrease in serum cholesterol or phospholipids (33).

The mechanism of these effects of saturated and unsaturated fats upon the level of serum lipids is still to be clarified. Knowledge regarding the relationship of unsaturated fatty acids to cholesterol metabolism has been summarized by Deuel (51). It is still undetermined whether the changes in plasma cholesterol and phospholipids noted above will result in prevention of or improvement in atherosclerosis. In terms of the total available knowledge, however, it would seem desirable to include a relatively high intake of unsaturated fat in the average dietary. Nuts are excellent sources of unsaturated fat. Of the commercially available salad and cooking oils, corn, cottonseed and soybean oil are rich in linoleic acid. The latter also contains 8% of linolenic acid. Much time will be required to determine whether the use of such dietary adjuvants will have preventive or therapeutic value in atherosclerosis.

Cholesterol

As previously noted, ingestion of very large amounts of dietary cholesterol by animals, which normally have little or no cholesterol in their diet, can produce pathological changes resembling human atherosclerosis. Consequently there has been much concern, unfortunately at times almost hysterical in nature, regarding inclusion of cholesterol-containing foods in human diets. There is as yet no final answer concerning this, nor will there be for some time. The following observations appear to be pertinent:

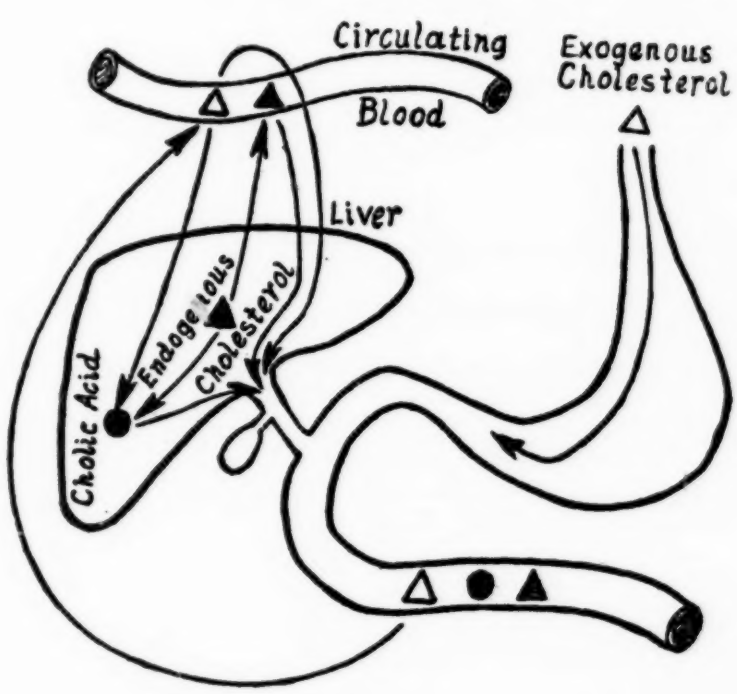
a. The average American diet is relatively high in cholesterol-containing foods, i.e. more or less fatty meats, gravies, eggs, dairy products, butter and cheese. The average daily cholesterol intake amounts to 250 to 800 milligrams (8). The amount of cholesterol required to produce atherosclerosis in rabbits or chickens, if corrected to human body weight, would amount to approximately 10 grams (10,000 milligrams) per day. It is apparent, therefore, that in terms of experimental comparisons our cholesterol intake is not high.

b. A number of peoples and tribes have been studied in regard to dietary intake and occurrence of atherosclerosis (9, 26). It is generally accepted that groups with a relatively low intake of cholesterol-containing foods, i.e. those with a high intake of foods which are not of animal origin, have a very much lower incidence of atherosclerosis. Some caution, however, must be used in interpreting these data; a majority of the people studied were relatively primitive. The laws of survival apply in a much more grim fashion in the

early years of these people than they do with us, and the stresses and strains of industrial civilization are completely absent.

c. Studies with normal (non-xanthomatosis) individuals have shown that synthesis of cholesterol by the body is low when the dietary cholesterol is high, and vice versa (34, 35, 36).

d. Friedman and his associates have done much to clarify our understanding of the relationship between cholesterol ingestion, endogenous cholesterol formation, cholesterol excretion, and cholesterol metabolism (37). Their observations, together with the recent observations in our laboratory noted above (31a), would lead us to believe that a major function of cholesterol (in cooperation with phospholipids, triglycerides, and certain of the plasma proteins) is that of transport of fatty acids between depots, the liver, and possibly peripheral tissues. An adequate supply of essential (unsaturated) fatty acids is necessary for proper functioning of this apparatus. If these concepts are correct, then dietary cholesterol is a factor of secondary importance, and dietary unsaturated fat, a primary factor.



SCHEMA OF CHOLESTEROL METABOLISM

Entities other than triglycerides present in dietary fat

Peterson first noted that addition of vegetable sterols to "atherogenic diets" in chicks prevented the development of atherosclerosis (38). This has been confirmed (39). Siperstein, Nichols and Chaikoff have reported that dihydrocholesterol produced the same effect (40). Both groups of investigators felt that the effects were attributable to inhibition of cholesterol absorption.

Best and his associates reported that β-sitosterol administered to human subjects receiving relatively uncontrolled mixed diets, resulted in significant lowering of serum cholesterol (41). There are numerous contradictory re-

ports. Wilkinson and his associates in a recent paper (42) pointed out that the changes observed by Best in serum cholesterol, associated with β-sitosterol administration, are no greater than those which they had observed in patients receiving no treatment, but studied over prolonged periods of time. Kinsell and his associates have administered large amounts of other vegetable sterols including mixed soy sterols, dihydrocholesterol, and stigmasterol to patients receiving chemically constant formula diets containing moderate and large amounts of fat (27, 30, 31, 43). Changes have been erratic, although in some instances significant decreases in cholesterol and phospholipids appear to have occurred. These investigators also have administered large amounts of soy phospholipids to patients under quantitatively controlled dietary conditions, and have noted similar erratic changes in the plasma cholesterol and phospholipid levels (43). Lecithin, administered to cholesterol-fed, depancreatectomized chicks, failed to modify the hypercholesterolemia (44).

Dietary carbohydrate

As yet, there is no indication that the carbohydrate level of the diet plays any significant role in regulating serum lipid level, or in the development of atherosclerosis. Excessive intake of carbohydrate, resulting in overnutrition and obesity, may of course be an important factor in the development of atherosclerosis. It has been demonstrated, however, that degenerative vascular disease occurs earlier and progresses more rapidly in the diabetic, as compared to the non-diabetic members of the population (10, 45). The reasons for this are still obscure.

Dietary protein

In the early experimental work dealing with atherosclerosis, it was demonstrated that rabbits fed meat, milk, or eggs developed the disease. Initially, protein was regarded as the responsible factor. Shortly thereafter, however, cholesterol-containing foods were specifically implicated (11a).

Generally speaking, populations which have a low intake of animal proteins (9, 25, 26, 46) have a low incidence of atherosclerosis, with the exception of the Eskimo in whom the animal protein (and fat) intake is high, and the incidence of cardiovascular disease is thought to be low (9). (Whale blubber and fish oils contain large amounts of arachidonic acid.) It should, however, again be pointed out that the laws of survival of the fittest in many such populations, result in a much higher infant and childhood mortality, and also in a lower adult life expectancy. Therefore such statistics must be interpreted with great caution.

Statistics obtained from a number of countries during the first and second world wars indicate that the incidence of deaths from degenerative cardiovascular disease fell significantly at a time when the intake of animal protein and of calories was restricted (6). In this connection, it must also be recognized that decrease in animal protein intake is associated almost without exception with a decrease in intake of animal fat.

At the present time there is no impressive evidence that protein intake is significantly related to atherogenesis, with the possible exception of the need for a minimal essential amount of methionine as a choline precursor and as an essential amino acid (16, 47).

Dietary minerals

At this time only sodium and potassium will be considered in relation to vascular disease. Calcium is a prominent component of the older atherosclerotic plaque, but it seems probable that this is a secondary rather than a primary factor. In the individual who is predisposed to hypertension, an elevated sodium intake increases the hypertension, partly by increase in blood volume and probably through other mechanisms as well. On the basis of experimental evidence, it appears that a high sodium intake will intensify a pre-existing tendency to atherosclerosis (48).

Potassium has not been shown to exert any effect upon plasma lipids or upon atherosclerosis. It is, however, implicated in certain aspects of lipid metabolism (49, 50), and it exerts a sodium diuretic effect when administered in adequate amounts. Therefore it may eventually be proven to play a role of some significance in the overall problem of atheromatosis.

Vitamins other than B_6

Reports relating to the effect of large dosage of vitamin D upon cholesterol-induced atherosclerosis are contradictory, but are probably related to choline deficiency (47).

Excess or deficiency of other specific vitamins have not as yet been proven to have any definite relationship to experimental or clinical atherosclerosis.

In summary, the problem of human atherosclerosis is still "wide open." Three positive statements are in order. First, hypernutrition; i.e., excessive caloric intake over a prolonged period of time, bears a highly significant relationship to degenerative vascular disease. Second, atherosclerosis occurs earlier and progresses more rapidly in the diabetic than in the non-diabetic. Third, experimental, and possibly clinical, atherosclerosis is reversible, if

treatment is instituted in time (11b). Emphasis however should be placed on prophylaxis rather than treatment.

A vast number of experimental studies show that in many species, atherosclerosis can be produced by feeding large amounts of cholesterol in conjunction with a diet that is otherwise usual for that particular species. This is so even in quite young animals. The combination of excessive cholesterol intake and deficiency of lipotropic agents can result in hyperlipemia and atherosclerosis in species in which cholesterol feeding alone will not produce atherosclerosis.

In the human subject, two dietary programs have been shown to produce a predictable and highly significant decrease in cholesterol levels; namely, hyponutrition (starvation or semistarvation), and administration of relatively large amounts of unsaturated fat. There is at least suggestive evidence that hyponutrition results in a decreased incidence of atherosclerosis. It is still unknown whether the relative or absolute hypocholesterolemia associated with the intake of unsaturated fats will result in a diminished incidence of atherosclerosis.

Until further knowledge is available, one might conclude that avoiding obesity, and ingesting a nutritionally adequate diet, containing more than 50 grams of unsaturated fat, would be advisable for the individual over the age of 35.

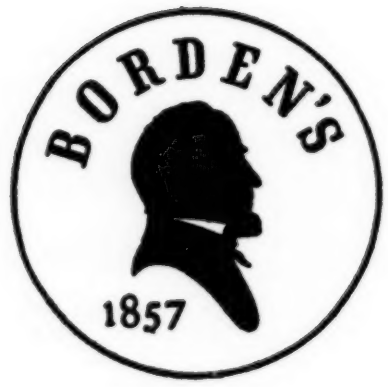
In conclusion, it seems to this reviewer that one of the major objectives of research in the fields of lipid metabolism and atherosclerosis should be the determination of the *normal functions* of cholesterol. Any molecule normally present in plasma in a concentration approaching 200 milligrams per 100 milliliters, is obviously of major metabolic importance. Yet, to date, its functions are undefined.

REFERENCES CITED

1. ANITSCHKOW, N. and Chalatow, S. *Centralbl. f. allg. Path. u. path. Anat., 24,* 1 (1913).
2. ANITSCHKOW, N. *Beitr. z. path. Anat. u. z. allg. Path., 56* 379 (1913).
3. KATZ, L. N., Stamler, J. Experimental Atherosclerosis. Charles C. Thomas, Springfield, Ill. (1953), pp. 258-261.
4. *Ibid:* pp. 25-43.
5. *Ibid:* pp. 173-189.
6. *Ibid:* pp. 25-32.
7. *Ibid:* pp. 203-208.
8. *Ibid:* p. 35.
9. *Ibid:* pp. 20-24.

10. *Ibid:* p. 43.
11a. *Ibid:* p. 5.
11b. *Ibid:* pp. 274-279.
12. MANN, G. V., Andrus, S. B., McNally, A., and Stare, F. J. *J. Exp. Med. 98,* 195 (1953).
13. MOON, H. D., and Rinehart, J. F. *Circulation 6,* 481-488 (1952).
31a. KINSELL, L. W., Friskey, R. W., Jr., Michaels, G. W., and Brown, F. *J. Clin. Nutrition.* In press.
14. MOVAT, H. Z., More, R H. *Circulation 12,* 484 (1955).
15. RINEHART, J. F., and Greenberg, L. D. *Am. J. Path. 25,* 481 (1949).
16. WILGRAM, G. F., Hartroft, W. S., Best, C. H. *Science 119,* 842 (1954).
17. WILGRAM, G. F., Hartroft, W. S., Best, C. H. *Brit. Med. J. 2,* 1 (1954).
18. WILGRAM, G. F., Best, C. H., and Lewis, L. A. *Circulation 12,* 490 (1955).
19. WILENS, S. L. *Arch. Int. Med. 79,* 129 (1947).
20. KEYS, A. *J. Chronic Dis. 1,* 456 (1955), (editorial).
21. FABER, M., and Lund, F. *Arch. Path. 48,* 351 (1949).
22. WALKER, W. J. *Ann. Int. Med. 39,* 705 (1953).
23. RUSS, E. M., Eder, H. A., and Barr, D. P. *Am. J. Med. 19,* 4 (1955).
24. WILKINSON, C. F., Blechs, E., and Reimer, A. *Arch. Int. Med. 85,* 389 (1950).
25. KEYS, A., Michelsen, O., Miller, E. V. O., and Chapman, C. B. *Science 112,* 79 (1950).
26. KEYS, A., Stewart, B. B., Brock, J. F., Moodie, A., Keys, M. H., and Antonis, A. *Circulation 12,* 492 (1955).
27. KINSELL, L. W., Partridge, J., Boling, L. A., Margen, S., and Michaels, G. D. *J. Clin. Endocrinol. and Metab. 12,* 909 (1952).
28. AHRENS, E. H., Jr., Blankenhorn, D. H., and Tsaltas, T. T. *Proc. Soc. Exper. Biol. and Med. 86,* 872 (1954).
29. BEVERIDGE, J. M. R., Connell, W. F., Mayer, G., Firstbrook, J. B., and DeWolfe, M. *Circulation 10,* 593 (1954).
30. KINSELL, L. W., and Michaels, G. D. *Fed. Proc. 14,* 661 (1955).
31. FRISKEY, R W., Michaels, G. D., and Kinsell, L. W. *Circulation 12,* 492 (1955).
32. LEVER, W. F., and Waddell, W. R. *J. Invest. Dermat. 25,* 233 (1955).
33. KINSELL, L. W., Cochrane, G. C., Coelho, M. A., and Fukayama, G. M. *Calif. Med. 81,* 218 (1954).
34. GOULD, R. G., Taylor, G. B., Hagerman, J. S., Warner, I., and Campbell, D. J. *J. Biol. Chem. 201,* 519 (1953).
35. COX, G. E., Nelson, L. G., Wood, W. B., and Taylor, C. B. *Fed. Proc. 13,* 31 (1954).
36. TAYLOR, C. B., Cox, G. E., Nelson, L. G., Davis, C. B., Jr., and Haas, G. H. *Circulation 12,* 489 (1955).
37. FRIEDMAN, M., Byers, S. O., and St. George, Shirley. Sterol Metabolism (in press).
38. PETERSON, D. W. *Proc. Soc. Exp. Biol. and Med. 78,* 143 (1951).
39. HERNANDEZ, H. H., and Chaikoff, I. L. *Proc. Soc. Exp. Biol. and Med. 87,* 541 (1954).
40. SIPERSTEIN, M. D., Nichols, C. W., Jr., and Chaikoff, I. L. *Circulation 7,* 37 (1953).
41. BEST, M. M., Duncan, C. H., Van Loon, E. J., Wathen, J. D. *Am. J. Med. 19,* 61 (1955).
42. LEVERE, A. H., Bozian, R. C., Jackson, R. S., and Wilkinson, C. F., Jr. *Circulation 12,* 483 (1955).
43. KINSELL, L. W., Michaels, G. D., Cochrane, G. C., Partridge, J. W., Jahn, J. P., and Balch, H. E. *Diabetes 3,* 113 (1954).
44. KATZ, L. N., and Stamler, J. Experimental Atherosclerosis. Charles C. Thomas, Springfield, Illinois, (1953), pp. 217-220.
45. LIEBOW, I. M., Hellerstein, H. K., and Miller, M. *Am. J. Med. 18,* 438 (1955).
46. MANN, G. V., Munoz, J. A., Scrimshaw, N. S. *Amer. J. Med. 19,* 25 (1955).
47. BUCKLEY, G. F., and Hartroft, W. S. *Am. J. Clin. Nutrition 2,* 396 (1954).
48. MENEELY, G. R., Lemly-Stone, J., Tucker, R. G., Blake, T. M., Auerbach, S. H., Darby, W. J., and Goodpasture, E. W. *Circulation 12,* 481 (1955).
49. KINSELL, L. W. *J. Lancet* (Symposium on Potassium Metabolism) *73,* 222 (June), (1953).
50. LARDY, H. A. *J. Lancet* (Symposium on Potassium Metabolism) *73,* 254 (June), (1953).
51. DEUEL, H. J., Jr. *Fed. Proc. 14,* 639 (1955).

VOL.
610
B7
N



Printed in U.S.A.